30

PATENT SPECIFICATION

NO DRAWINGS

902,658

Date of Application and filing Complete Specification: Jan. 10, 1961.

No. 991/61.

Application made in United States of America (No. 58632) on Sept. 27, 1960

Complete Specification Published: Aug. 9, 1962.

Index at acceptance:—Class 2(3), C1C(3:5:9:10:11F), C1J1(A7:A9:B:C3), C2D43(F:J:L:S4)

International Classification:—C07d.

COMPLETE SPECIFICATION

6-Substituted (or unsubstituted) 2-Alkyl-3-Allylthiomethyl-7-Sulphamyl-3,4-Dihydrobenzothiadiazine Dioxides and process for preparation

We, CHAS. PFIZER & CO., INC., a corpora-

ERRATA

SPECIFICATION NO. 902,658

Page 2, line 25, *for* "chloro-" *read* "chloro,"

Page 2, line 60, *for* "methods, for" *read* "methods. For"

Page 2, line 75, *after* "such" *insert* "as"

Page 3, line 54, *for* "pharmacologicallyacceptablecations" *read* "pharmacologically acceptable cations"

Page 4, line 49, *for* "2-m-propyl" *read* "2-*n*-propyl"

THE PATENT OFFICE,
24th September, 1962

DS 67751/1(20)/R.109 200 9/62 PL

wherein A is hydrogen, Cl, Br, trifluoromethyl or alkyl or alkoxy, each containing 1 to 3 carbon atoms, and R is lower alkyl of 1 to 6 carbon atoms.

It is also intended to include within the scope of this invention salts of the above class of compounds. Particularly valuable are salts formed with bases containing a pharmacologically acceptable cation.

The 6 - substituted (or unsubstituted) -2-alkyl - 3 - allylthiomethyl - 7 - sulphamyl-3,4 - dihydrobenzothiadiazine dioxides of this invention may be prepared by

(a) condensing a disulphonamide of the following general formula:

example, lower-alkyl acetals of these aldehydes, which may be generally represented by the formula

$$CH_2=CHCH_2SCH_2CH(OR_1)_2$$

in which R_1 is lower alkyl. The reaction is preferably effected by heating a substantially equimolar mixture of the reactants in an inert organic solvent at a temperature of from about 60° C. to about 120° C. Usually, a reaction time of from about ½ to about 5 hours is found to give excellent yields of the desired products. Longer reaction time may be used without appreciable advantage. Slight excess of aldehyde, or derivative, for example up to 10% may be used, but larger excesses should be

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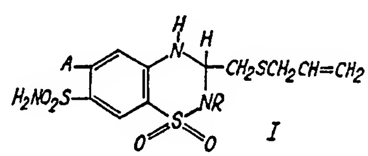
6-Substituted (or unsubstituted) 2-Alkyl-3-Allylthiomethyl-7-Sulphamyl-3,4-Dihydrobenzothiadiazine Dioxides and process for preparation

We, CHAS. PFIZER & Co., INC., a corporation organised under the laws of the State of Delaware, United States of America, of 11 Bartlett Street, Brooklyn, State of New York, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention is concerned with a new class of highly effective therapeutic agents as well as the method of preparing same. In particular the therapeutic agents of this invention are 6-substituted (or unsubstituted) -2-alkyl-3 - allylthiomethyl - 7 - sulphamyl - 3,4 - dihydrobenzo - 1,1 - dioxo - 1 - thia - 2,4-diazines. The compounds, hereinafter referred to as 6-substituted (or unsubstituted)-2-alkyl-3 - allylthiomethyl - 7 - sulphamyl - 3,4-dihydrobenzothiadiazine dioxides are represented by the following formula:



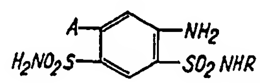
I

wherein A is hydrogen, Cl, Br, trifluoromethyl or alkyl or alkoxy, each containing 1 to 3 carbon atoms, and R is lower alkyl of 1 to 6 carbon atoms.

It is also intended to include within the scope of this invention salts of the above class of compounds. Particularly valuable are salts formed with bases containing a pharmacologically acceptable cation.

The 6 - substituted (or unsubstituted) -2-alkyl - 3 - allylthiomethyl - 7 - sulphamyl-3,4 - dihydrobenzothiadiazine dioxides of this invention may be prepared by

(a) condensing a disulphonamide of the following general formula:



II

wherein A and R are as hereinabove defined with an aldehyde, or the lower alkyl acetal or hemiacetal thereof, said aldehyde having the following general formula:

$$Y—CH_2CH=O \qquad \ldots III$$

wherein Y is the allylmercapto group of the formula

$$CH_2=CH—CH_2—S—$$

or is a halogen atom or an alkyl or aryl sulphonyloxy residue.

(b) and, when required, converting Y to the allylmercapto group by the condensation of the product of step (a) with allyl mercaptan.

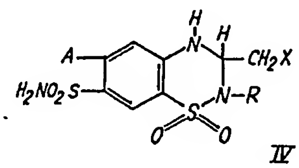
The corresponding aldehyde derivatives may be employed in place of the aldehyde, for example, lower-alkyl acetals of these aldehydes, which may be generally represented by the formula

$$CH_2=CHCH_2SCH_2CH(OR_1)_2$$

in which R_1 is lower alkyl. The reaction is preferably effected by heating a substantially equimolar mixture of the reactants in an inert organic solvent at a temperature of from about 60° C. to about 120° C. Usually, a reaction time of from about ½ to about 5 hours is found to give excellent yields of the desired products. Longer reaction time may be used without appreciable advantage. Slight excess of aldehyde, or derivative, for example up to 10% may be used, but larger excesses should be

avoided since their use may lead to reduced yield of the desired product.

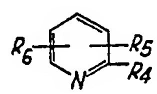
Also in accordance with this invention, the compounds of formula I may be prepared by condensing 3 - haloalkylbenzothiadiazine dioxide



IV

wherein A and R are as hereinabove defined and X is halogen or an alkyl or aryl sulphonyloxy residue with allyl mercaptan.

This reaction is generally carried out by contacting the above described 3 - (haloalkyl)-dihydrobenzothiadiazine dioxides with the selected thiol in the presence of a strong base, preferably alkali or alkaline earth metal hydroxides. Organic bases, such as sterically-hindered tertiary amines may also be employed. Preferred are mono-, di- and tri-substituted pyridines, represented by the formula:



wherein R_4 is selected from chloro, bromo and alkyl containing 1 to 3 carbon atoms and R_5 and R_6 are each selected from hydrogen, chloro- bromo and alkyl containing 1 to 3 carbon atoms. These are preferred since best results are obtained when they are used. Other sterically-hindered tertiary amines may also be employed in this process.

The metal hydroxide is best utilized in the form of an aqueous solution generally containing from about 5% to about 20% by weight of hydroxide although from 5% to 15% is preferred since best yields are obtained. While the reaction proceeds satisfactorily in aqueous solution, the addition of an organic solvent materially facilitates production of desired compounds by providing a more intimate contact of the reactants which have a limited solubility in water. Organic solvents useful in this respect are ketones such as acetone and ethyl methyl ketone, lower alkanols such as methanol, ethanol and the propanols, and, preferably dimethylformamide and similar lower alkylated formamides.

Although an equimolar ratio of reactants is found to yield appreciable amounts of product, it is generally preferred to employ excess thiol to obtain best yields. Excess of up to about 40 mole percent are found particularly suitable, while larger excesses, although operable, provide no appreciable advantage.

The reaction may be advantageously carried out at temperatures of from 20° to 120° C. for from about 1 to 12 hours. Heating at higher temperatures and for longer periods of time may lead to reduced yield of the desired product.

After the reaction is complete, the product may be obtained by conventional methods, for example, the product precipitates from the reaction mixture on cooling, is separated and purified by recrystallization from appropriate solvents, such as acetone, lower alkanols, acetone-ether mixtures, acetone-alkanol mixtures and the like.

By inert organic solvents as employed herein is meant an organic solvent which dissolves the reactants but does not react with same under the reaction conditions described. Such solvents may be readily determined by routine experimentation in the laboratory. Although other solvents may be employed, excellent results are obtained with N,N-dialkyl-loweralkanoamides, such dimethylformamide, diethylacetamide, dipropylpropionamide, diethylformamide and the like, as well as alkylated glycols, such as the dimethyl ether of butylene glycol, the dipropyl ether of ethyleneglycol and the like. When the acetals are used in place of the aldehydes, it is generally found helpful, but not essential, to add a minor amount of aqueous mineral acid. Usually only a few drops of aqueous acid, such as hydrochloric, sulphuric, phosphoric and the like, is found sufficient. The addition of acid merely increases the rate of reaction.

After the reaction is complete, the products are obtained by conventional methods, such as concentration and crystallization. The products may then be recrystallized from suitable solvents.

The present new compounds are found to be diuretic agents of high potency. They not only effect an increase in urine excretion but also effect a more favorable electrolyte excretion pattern with increased natriuresis and chloruresis without a commensurate increase in kaliuresis. This electrolyte excretion pattern is highly desirable since, as is generally known in the medical art, the use of many of the more potent diuretic agents generally leads to depletion of potassium in the body which condition is known as hypokalemia. Further, the present new compounds also exhibit a more prolonged duration of action and, therefore, a greater total effect on the basis of maximal rates of saluresis when compared with related known diuretics such as corresponding compounds in which the 2-substituent is hydrogen. For example, 2-methyl-3 - allylthiomethyl - 6 - chloro - 7 - sulphamyl - 3,4 - dihydrobenzthiazide - 1,1 - dioxide in rats shows greater diuresis, natriuresis and chloruresis and lower kaliuresis than 3 - allylthiomethyl - 6 - chloro - 7 - sulphamyl - 3,4 - dihydrobenzothiadiazine - 1,1-

dioxide and also exhibits a longer duration of action.

The therapeutic agents of this invention may be administered alone or in combination with pharmaceutically acceptable carriers, the proportion of which is determined by the solubility and chemical nature of the compound, chosen route of administration and standard pharmaceutical practice. For example, they may be administered orally in the form of tablets or capsules containing such excipients as starch, milk sugar, certain types of clay and so forth. They may be administered sublingually in the form of troches or lozenges in which the active ingredient is mixed with sugar and corn syrups, flavoring agents and dyes; and then dehydrated sufficiently to make it suitable for pressing into a solid form. They may be administered orally in the form of solutions which may contain colouring and flavouring agents or they may be injected parenterally, that is intramuscularly, intravenously or subcutaneously. For parenteral administration they may be used in the form of a sterile solution containing other solutes, for example enough saline or glucose to make the solution isotonic.

The physician will determine the dosage of the present therapeutic agents which will be most suitable and it will vary with the form of administration and the particular compound chosen, and furthermore, it will vary with the particular patient under treatment. He will generally wish to initiate treatment with small dosages substantially less than the optimum dose of the compound and increase the dosage by small increments until the optimum effect under the circumstances is reached. It will generally be found that when the composition is administered orally, larger quantities of the active agent will be required to produce the same effect as a smaller quantity given parenterally. The compounds are useful in the same manner as other diuretics and the dosage level is of the same order of magnitude as is generally employed with these other therapeutic agents. The therapeutic dosage will generally be from 1 to 10 milligrams per day and higher although it may be administered in several different dosage units. Tablets containing from 0.5 to 10 mg. of active agents are particularly useful.

In the foregoing, reference is made to pharmacologically acceptable cations. "Pharmacologically acceptable cations" has a definite meaning to one skilled in the art. It is defined as a non-toxic cation of basic compounds commonly used in pharmacology to neutralize acid medicinal agents when the salt thereof is to be used therapeutically. The pharmacological activity of the molecule is primarily a function of the anion, the cation serving chiefly to supply electrical neutrality. Commonly employed pharmacologically acceptable cations are, for example, sodium, potassium, calcium and magnesium. The salts of the compound of the present invention may be prepared employing conventional procedures. One such procedure involves treating the subject compounds with an aqueous solution containing an equivalent amount of the reagent, i.e. the pharmacologically acceptable base, followed by concentration of the resultant mixture to obtain the desired product. Pharmacologically acceptable bases are those which contain the cations described above. Such bases may be for example, oxides, hydroxides, carbonates or bicarbonates. Of course, salts formed with pharmacologically unacceptable bases, while not useful therapeutically, may be used in the purification of the present therapeutic agents and also in the preparation of the pharmacologically acceptable salts.

The starting compounds of the present process, i.e. the 4 - amino - 2 - substituted - 5-alkylsulphamylbenzenesulphonamides, are prepared according to known procedures, e.g. J.A.C.S. 82, 1132—1135 (1960).

The following examples are given by way of illustration and are not to be construed as limitations of this invention many variations of which are possible without departing from the scope and spirit thereof.

EXAMPLE I.

2 - Methyl - 3 - allylthiomethyl - 6 - chloro-7 - sulphamyl - 3,4 - dihydro - 1,2,4-benzothiadiazine - 1,1 - dioxide.

To 6.75 g. (0.0225 mole) of 4-amino-2-chloro - 5 - (methylsulphamyl)benzenesulphonamide in 45 ml. of dimethylformamide is added 4.86 g. (0.03 mole) of dimethyl allylmercaptoacetal followed by 1.5 ml. of ethyl acetate saturated with hydrogen chloride gas. The solution is refluxed for 1.5 hours, cooled and added dropwise with stirring to ice/water. The resulting precipitate is filtered, dried and recrystallized from isopropanol. Three recrystallizations gave 4.0 g. of product melting at 168.5°—170° C.

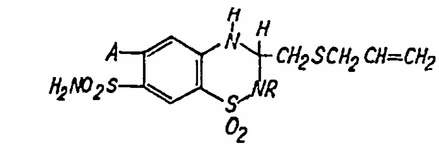
EXAMPLE II.

2 - Methyl - 3 - allylthiomethyl - 6 - methyl-7 - sulphamyl - 3,4 - dihydro - 1,2,4-benzothiadiazine - 1,1 - dioxide.

To a solution of 0.02 mole of 4 - amino-2 - methyl - 5 - (methylsulphamyl)benzenesulphonamide in 50 ml. of dimethylformamide is added 0.03 mole of dimethyl allyl mercaptoacetal followed by 1.5 ml. of ethyl acetate saturated with hydrogen chloride gas. The solution is refluxed for 2.0 hours, cooled and added dropwise with stirring to ice/water. The resulting precipitate is filtered, dried and recrystallized from isopropanol.

EXAMPLE III.

Employing the procedure of Example I the following compounds are prepared from corresponding starting compounds:



A	R
CF_3	CH_3
Br	C_2H_5
OCH_3	CH_3
n—C_3H_7	n—C_3H_7
OC_3H_7	i—C_3H_7
i—C_3H_7	CH_3

EXAMPLE IV.

The sodium salt of the Example I product is obtained by dissolving the product in water containing a molar equivalent of sodium hydroxide and then freeze-drying the mixture.

In this manner, the potassium, calcium and magnesium salts are also prepared.

EXAMPLE V.

A tablet base is prepared by blending the following ingredients in the proportion by weight indicated:

Sucrose U.S.P.	82.0
Tapioca starch	13.6
Magnesium stearate	4.4

Into this base there is blended a sufficient amount of 2 - methyl - 3 - allylthiomethyl-6 - chloro - 7 - sulphamyl - 3,4 - dihydro-1,2,4 - benzothiadiazine - 1,1 - dioxide to provide tablets containing 0.5, 2.5 and 10 mg. respectively of active ingredient.

EXAMPLE VI.

A mixture of 3 (chloromethyl) - 6 - chloro-7 - sulphamyl - 3,4 - dihydrobenzothiadiazine-1,1-dioxide (0.02 mole) and allyl mercaptan (0.024 mole) in 20 ml. of 10% sodium hydroxide and 20 ml. of dimethylformamide is stirred at room temperature for 6 hours. After heating for 10 minutes on a steam bath, the mixture is cooled and acidified with 6N HCl. The product, after recrystallization from acetone, melts at 206—207° C.

The compounds described in Example II and III are also prepared by this method from the corresponding intermediates.

EXAMPLE VII.

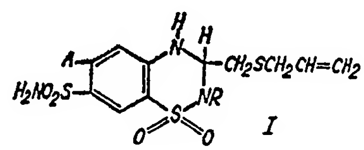
The procedure of Example VI is repeated employing, in place of sodium hydroxide, the following bases: potassium hydroxide, barium hydroxide, lithium hydroxide, calcium hydroxide, 2-chloropyridine, 2-bromopyridine, 2-methylpyridine, 2-i-propyl and 2-m-propylpyridine, 2,4-lutidine, 2,6-lutidine, 2,4-dichloropyridine, 2 - methyl - 4 - ethylpyridine, 4 - chloro - 2 - methylpyridine and 2,4,6-collodine, with comparable results.

EXAMPLE VIII.

The procedure of Example VI was carried out using 3 - (tosylmethyl) - 6 - chloro - 7-sulphamyl - 3,4 - dihydrobenzothiadiazine-1,1 - dioxide instead of the 3 - (chloromethyl)-6 - chloro - 7 - sulphamyl - 3,4 - dihydrobenzothiadiazine - 1,1 - dioxide with comparable results.

WHAT WE CLAIM IS:

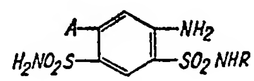
1. A process for preparing 6 - substituted (or unsubstituted) -2 - alkyl - 3 - allylthiomethyl - 7 - sulphamyl - 3,4 - dihydrobenzothiadiazine dioxide of the formula:



I

wherein A is hydrogen, Cl, Br, trifluoromethyl or alkyl or alkoxy, each containing 1 to 3 carbon atoms, and R is lower alkyl of 1 to 6 carbon atoms, characterized by

(a) condensing a disulphonamide of the following general formula:



II

wherein A and R are as hereinabove defined with an aldehyde, or the lower alkyl acetal or hemiacetal thereof, said aldehyde having the following general formula:

$$Y—CH_2CH=O \quad \ldots III$$

wherein Y is the allylmercapto group of the formula

$$CH_2=CH—CH_2—S—$$

or is a halogen atom or an alkyl or aryl sulphonyloxy residue,

(b) and, when required, converting Y to the allylmercapto group by the condensation of the product of step (a) with allyl mercaptan.

2. A process according to claim 1, characterized by the fact that the aldehyde has the formula

$$CH_2=CH—CH_2SCH_2CH=O \ldots IIIA$$

3. A process according to claim 1 or 2, characterized by the fact that in step (a) sub-

stantially equimolar amounts of reactants are used.

4. A process according to any one of the preceding claims, characterized by the fact that the reaction is carried out in an inert solvent.

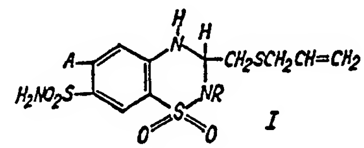
5. A process according to any one of the preceding claims, characterized by the fact that the reaction is effected at a temperature in the range of 60° C. to 120° C.

6. A process according to any one of the preceding claims, characterized by the fact that the reaction in step (a) is effected in the presence of an acid.

7. A process for preparing 6 - substituted (or unsubstituted) -2 - alkyl - 3 - allylthiomethyl - 7 - sulphamyl - 3,4 - dihydrobenzothiadiazine dioxides substantially as described.

8. 6-Substituted (or unsubstituted) -2-alkyl-3 - allylthiomethyl - 7 - sulphamyl - 3,4 - dihydrobenzothiadiazine dioxides whenever prepared by the process substantially as described.

9. 6-Substituted (or unsubstituted) -2-alkyl-3 - allylthiomethyl - 7 - sulphamyl - 3,4-dihydrobenzothiadiazine dioxides of the formula:



I

wherein:

A is chloro, bromo, trifluoromethyl or alkyl or alkoxy each containing 1 to 3 carbon atoms; and R is lower alkyl of 1 to 6 carbon atoms; and salts thereof with pharmacologically acceptable bases.

10. 2 - Methyl - 3 - allylthiomethyl - 6-chloro - 7 - sulphamyl - 3,4 - dihydro - 1,2,4-benzothiadiazine - 1,1 - dioxide.

11. 2 - Methyl - 3 - allylthiomethyl - 6-methyl - 7 - sulphamyl - 3,4 - dihydro - 1,2,4-benzothiadiazine - 1,1 - dioxide.

STEVENS, LANGNER, PARRY & ROLLINSON,
Chartered Patent Agents,
Agents for the Applicants.

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